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Case report

Resolution of ictal bradycardia and asystole following temporal lobectomy: A case report, and review of available cases using pacemakers

Stephanie Ballendine [a], Izn Shahab [a], Mitzel Perez-Careta [b], Francisco J. Taveras-Almonte [b], Iris E. Martínez-Juárez [c], Laura E. Hernández-Vanegas [c], Chelsea Dolinsky [d], Adam Wu [e], Jose Francisco Tellez-Zenteno [a,*]

[a] Division of Neurology, Department of Medicine, University of Saskatchewan, Saskatoon, Canada
[b] Clinical Epileptology Fellowship, National Institute of Neurology and Neurosurgery, Mexico City, Mexico
[c] Epilepsy Clinic, National Institute of Neurology and Neurosurgery, Mexico City, Mexico
[d] Neurophysiology Laboratory at Royal University Hospital, Saskatoon, Saskatchewan, Canada
[e] Division of Neurosurgery, Department of Medicine, University of Saskatchewan, Saskatoon, Canada

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ABSTRACT

Ictal bradycardia (IB) and ictal asystole (IA) are uncommonly recognized phenomena that increase morbidity in patients with epilepsy by causing syncope and seizure-related falls. These arrhythmias are also suspected to be involved in the pathophysiology of sudden unexpected death in epilepsy (SUDEP). We report a case of a 57-year-old male with left temporal lobe epilepsy who experienced both IB and IA. This patient was initially managed with pacemaker implantation, prior to undergoing left temporal lobectomy. Following surgery, the patient had no ongoing IB or IA on his pacemaker recordings, and his seizure control was greatly improved. His pacemaker was removed approximately one year post-operatively and he continued treatment with anti-seizure drugs (ASDs). A literature review of cases of IB and IA that were managed with pacemakers was performed. Pacemaker implantation appears to be quite effective for reducing seizure-related syncope and falls in the setting of IB/IA. Epilepsy surgery also seems to be an effective treatment option for IB/IA, as many patients are able to have their pacemakers removed post-operatively. Further investigations into the pathophysiology of IB and IA and long-term outcomes using different treatment modalities are clearly needed to help formulate treatment guidelines and, potentially, to reduce the occurrence of SUDEP in these patients.

1. Introduction

Ictal arrhythmias including ictal bradycardia (IB) and ictal asystole (IA) occur frequently in patients with epilepsy [2], although they may go unrecognized by clinicians. These arrhythmias are induced by ictal activity via mechanisms that remain poorly understood. The effects of these arrhythmias in patients with epilepsy also remain to be fully characterized. Research has shown that IB and IA cause syncope and seizure-related falls, which significantly increase patient morbidity [9]. It is also possible that these arrhythmias contribute to the pathophysiology of sudden unexpected death in epilepsy (SUDEP). Preventing these adverse events from occurring is of upmost importance for clinicians treating patients with epilepsy.

Treatment strategies for ictal arrhythmias include antiseizure drugs (ASDs) and epilepsy surgery, to reduce seizure frequency, and pacemaker (PM) implantation to manage arrhythmias. A prior review examining patients with IA found high rates of ASD resistance [3], indicating that medical management alone will often be inadequate. The outcomes of epilepsy surgery on ictal arrhythmias have not been well researched and require further investigation. PM implantation seems to be a reasonable strategy to prevent adverse outcomes from ictal arrhythmias. However, the most effective management for ictal arrhythmias remains unknown, and there are currently no established treatment guidelines. Given the increases in morbidity and, possibly, mortality associated with ictal arrhythmias, treatment guidelines are essential.

To provide insight into these issues, we present a case of a patient with IB and IA that were managed with PM implantation and, ultimately, temporal lobectomy. A literature review of available cases using PMs for ictal arrhythmias was also performed to assess patient outcomes with this treatment strategy. Existing clinical research

Abbreviations: IB, ictal bradycardia; IA, ictal asystole; SUDEP, sudden unexpected death in epilepsy.

* Corresponding author at: Division of Neurology, Department of Medicine, Royal University Hospital, 103 Hospital Drive. BOX 26, Room 1622, Saskatoon, SK S7N OW8, Canada.
E-mail address: jose.tellez@usask.ca (J.F. Tellez-Zenteno).

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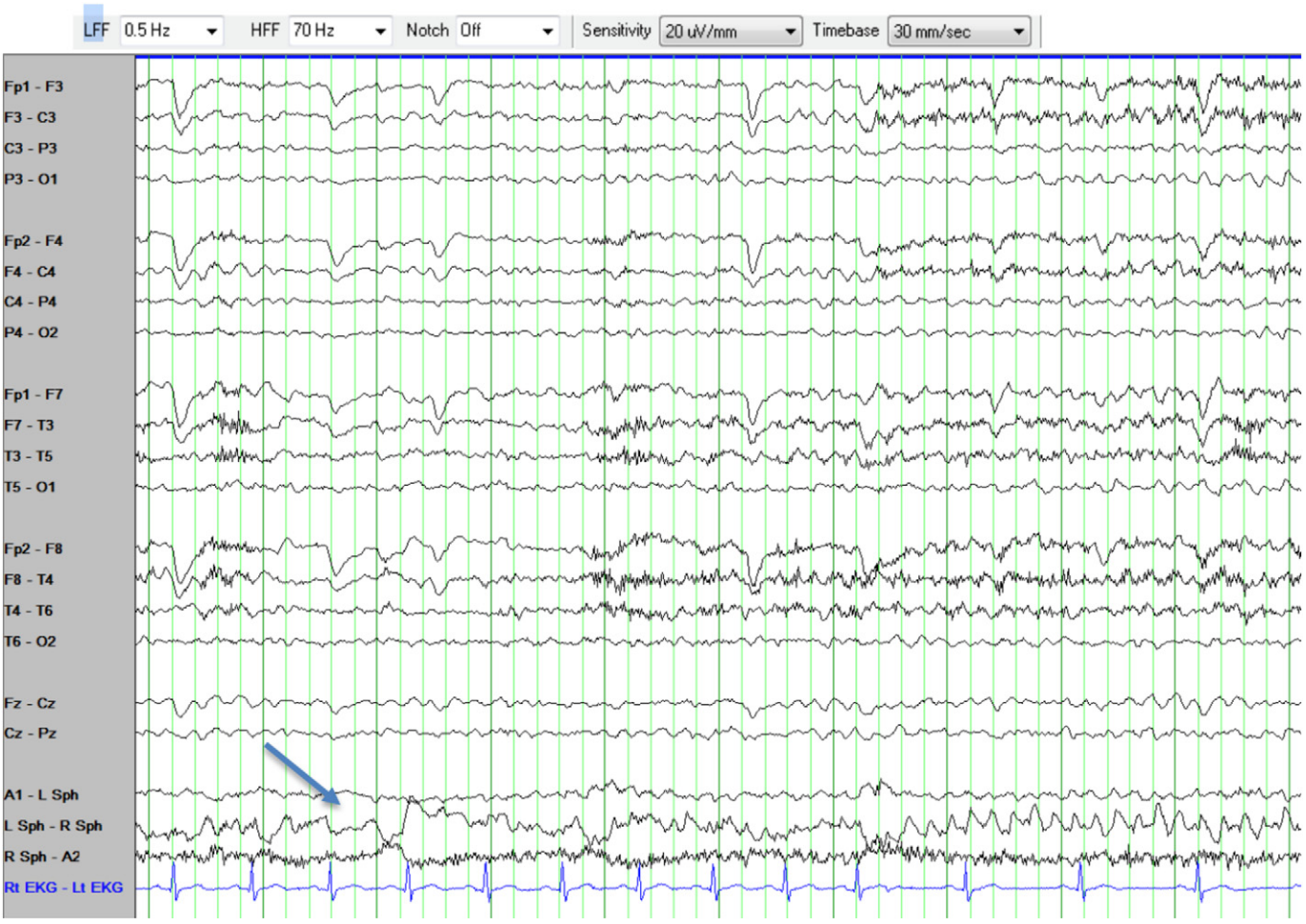

Fig. 1. Title: EEG showing seizure onset. Onset of the seizure at the left sphenoidal electrode (bipolar montage) without significant concurrent ECG changes.

suggests that PM implantation should probably be performed more frequently in patients with ictal arrhythmias to prevent adverse cardiac events and, potentially, to decrease the likelihood of SUDEP.

2. Case presentation

This case describes an otherwise healthy 57-year-old right-handed gentleman who had drug-resistant epilepsy since the age of eleven. His history was significant for the presence of focal impaired awaraeness seizures that lasted for less than 1 min. The patient described experiencing autonomic features including an epigastric sensation, dizziness and occasional presyncope followed by prominent blinking, unresponsiveness and post-ictal confusion. He rarely experienced focal to bilateral tonic–clonic seizures. He denied ever having experienced a clear syncopal event.

On presentation, the patient was found to have a normal neurological examination. His seizures were deemed clinically to be consistent with a temporal lobe origin (more mesial). He had previously failed several ASDs including vigabatrin (VGB) and gabapentin (GPB). His ASD regimen consisted of topiramate (TPM) 300 mg twice a day, phenytoin (PTH) 500 mg a day and phenobarbital (PB) 150 mg twice a day. Despite treatment with multiple antiseizure medications he had approximately one seizure per month. The patient had a motor vehicle accident due to a seizure, but was otherwise highly functional, was employed and had a family.

Due to the presence of drug-resistant epilepsy, he was assessed as a candidate for epilepsy surgery. On video-EEG telemetry, performed with ASD withdrawal, eight focal seizures were recorded; three seizures were focal to bilateral tonic–clonic. Interictal EEG showed intermittent mild to moderate slowing over the left temporal region in the frequency of theta and delta, in keeping with a functional or structural abnormality, in addition to left anterior temporal spikes. All recorded seizures had a clear onset at the left temporal region (maximum at F7 and T3) (Fig. 1). All seizures began with rhythmic theta-delta waves that were at times sharply contoured, with involvement of F7, T3 and the left sphenoidal electrodes. These waves evolved into sharp wave potentials at 3–4 Hz in the same location, followed by spread to the left parasagittal electrodes. EEG waves changed to lower voltage delta and theta waves prior to returning to baseline. The focal seizures lasted 30 to 110 s. For focal seizures that generalized, the focal portion lasted approximately 10 s followed by 60 s of generalized activity (Fig. 1). The semiology of the seizures recorded during video-EEG telemetry was similar to the clinical description of patient, and in keeping with a temporal lobe origin. The patient typically displayed prominent blinking, unresponsiveness, head deviation to the right, left hand automatisms and post-ictal confusion.

In all of the documented seizures the patient consistently developed IB (with an ictal heart rate of 30 beats per minute (BPM)) and periods of IA (lasting up to 8 s) approximately 3 to 4 s after the EEG onset (Fig. 2). The patient's heart rate consistently returned to normal range (60–100 BPM) when the seizure activity ended. He denied any cardiac symptoms during these episodes of IB/IA. These concerning findings prompted a referral to Cardiology for PM implantation.

An MRI of the patient's brain demonstrated normal, symmetric hippocampi with no atrophy or signal change. However, it did show extensive bilateral white matter changes. This extensive white matter disease

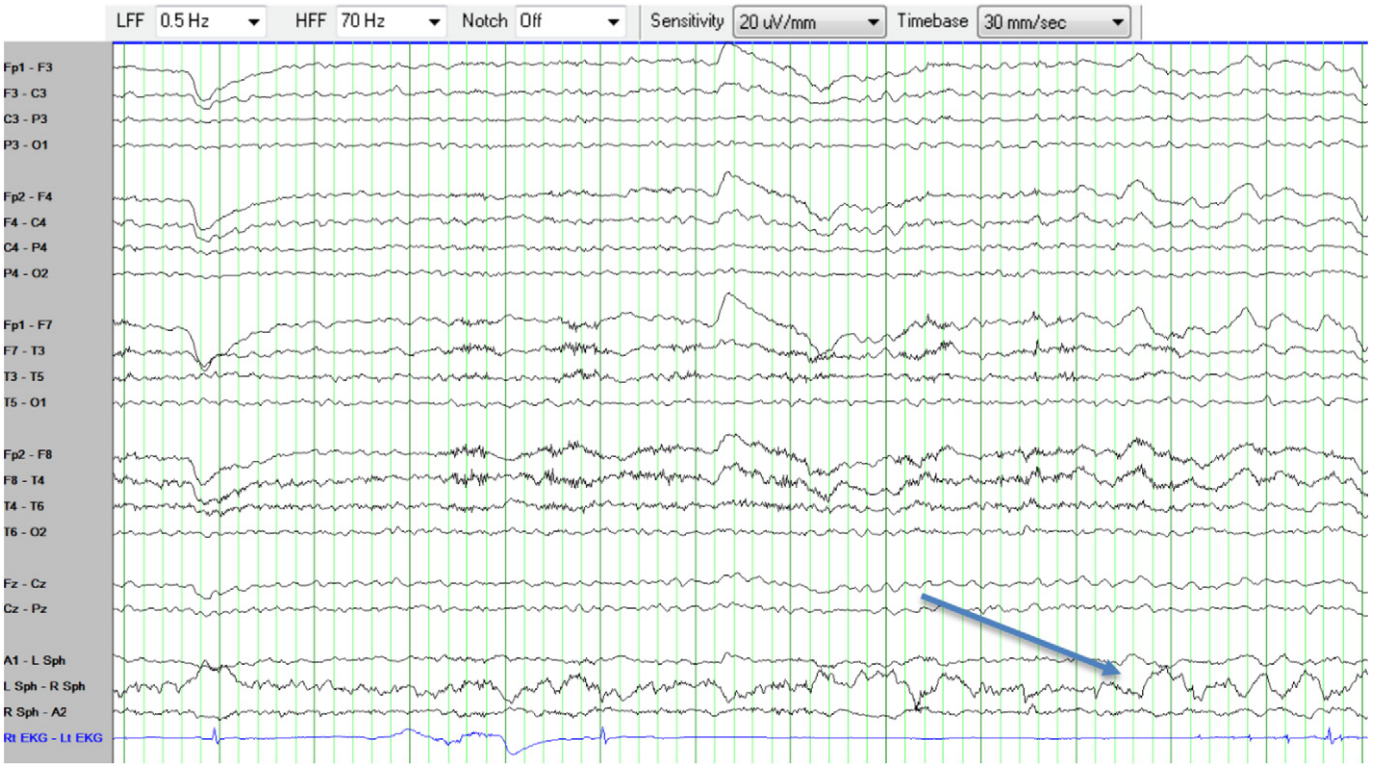

Fig. 2. Title: EEG showing ictal bradycardia. 15 s after seizure onset, severe bradycardia develops and continuous changes at the left sphenoidal electrode can be seen (bipolar montage).

caused concern that the patient could be at significant risk of memory impairment following epilepsy surgery. This concern was increased when the patient's neuropsychiatric testing demonstrated significantly and globally compromised cognitive function. Specifically, there were found to be limitations in verbal comprehension, perceptual reasoning ability, working memory and processing speed. The patient was moderately below average in confrontation naming and semantic and phonemic fluency. Learning and memory skills were extremely impaired globally. It is likely that the patient's ASD regimen also contributed to his cognitive impairments, though this effect was difficult to quantify. A functional MRI lateralized the patient's language to the left hemisphere. A PET scan showed hypometabolism over the left temporal region. We considered that he did not require a second phase involving intracranial EEG (stereo-EEG) as scalp EEG, PET scan, and neuropsychological testing were localizing and lateralizing to the left temporal region.

During the nine months that the patient had a PM prior to his epilepsy surgery, the PM discharged six times. All of the discharges occurred during seizures for concurrent episodes of IB lasting between 10 and 12 s. No tachycardia or other worrisome arrhythmia was identified. After discussing the risks of surgery, the patient agreed to undergo a left standard temporal lobectomy. Pathology results from the resection were consistent with gliosis in the medial temporal lobe, as well as in the neocortical structures.

In the immediate postoperative period, the patient developed aphasia with impaired naming and word finding difficulties, but preserved fluency. His language improved over time with the aid of speech therapy. The patient's wife also reported a mild increase in the patient's aggression following surgery. Postoperative cognitive testing indicated only mild changes in cognitive function. Routine postoperative EEGs demonstrated intermittent left temporal slowing, consistent with post-surgical changes, but no ongoing epileptiform activity.

Since undergoing left temporal lobectomy, the patient has been seizure free for six years. He was able to discontinue TPM and reduce the dosage of both PB and PTH. His current ASD regimen consists of PB 30 mg three times a day, PTH 100 mg in the morning and 200 mg at night and clobazam (CLB) 10 mg twice a day. Along with seizure freedom, temporal lobectomy resulted in resolution of the patient's arrhythmias. Recordings from his PM in the year following surgery showed no evidence of bradycardia or asystole. The PM was removed approximately one year after temporal lobectomy and the patient continued to do well, with no ongoing cardiac concerns.

3. Literature review

We performed a literature search and reviewed all of the available cases where a PM was placed for IB or IA from 1986 to 2018. Ninety cases of IB/IA requiring PM implantation were identified (Table 1). Analysis of the 90 cases showed that IB/IA was discovered using video-EEG in 51 cases (56.7%). Patients' mean age was 47.33 years (±15.7); 43 patients (84.3%) were males. Consistent with our patient's presentation, 81 (90%) of the 90 reviewed cases had temporal lobe epilepsy, with a predominance of epileptic activity on the left side in 40 patients (44.4%). Eighty-two (91%) cases were medically managed with ASD monotherapy, using a wide variety of ASDs. One patient was treated with polytherapy. Many patients required changes to their ASD regimen, with dose adjustment being performed most commonly.

In forty-eight (53%) cases, bradycardia was experienced before seizure onset. The most significant bradycardia recorded was 30 BPM (±10). The average duration of IA was 15.6 s (±11.7). Three patients (3.3%) were treated with the exclusive use of a PM while the majority of patients (82/91.1%) were treated with a PM and ASDs. The ASDs that were most commonly used in patients with PMs were levetiracetam (LEV) in 30 patients (33.3%), followed by carbamazepine (CBZ) in 19 patients (21.1%), lamotrigine (LTG) in 17 patients (18.9%) and PTH in 16 patients (17.8%). Less frequently used ASDs included valproate (VPA) in 12 patients (13.3%), oxcarbazepine (OXC) and TPM in 8 patients (8.9%) each; PB, GPB, clonazepam (CLZ) and CLB in 3 patients (3.3%) each; and zonisamide (ZNS) in only 2 patients (2.2%).

Overall, seizure outcome data from all of the reviewed cases showed that 28 patients (31.1%) were seizure free, 22 (24.4%) continued to have

Table 1
Title: Literature review data.
Data obtained from patients with IB/IA managed with pacemaker implantation (1986–2018). The follow up in studies ranged from 6 months to a year.

IB/IA + Pacemaker	n = 90
Age	47.33 (±15.75)
Male/female	43 (47.8%)/33 (36.7%)
Unknown gender	14 (15.6%)
Onset (localization)	
Right/left temporal lobe	25 (27.8%)/40 (44.4%)
Temporal (unknown side)	16 (17.8%)
Extratemporal	9 (10%)
Treatment	
No surgery	83 (92.2%)
Surgery: before/after pacemaker	1 (1.1%)/6 (6.7%)
Medical treatment/number of ASD	1 (0–5)
LEV/CBZ	30 (33.3%)/19 (21.1%)
LTG/PTH	17 (18.9%)/16 (17.8%)
VPA/OXC, TPM (EACH)	12 (13.3%)/8 (8.9%)
PB, GPB, CLB, CLZ (EACH)/ZNS	3 (3.3%)/2 (2.2%)
LCS, PRM, TGB (EACH)	1 (1.1%)
Final treatment	
Only pacemaker/ASD	3 (3.3%)/5 (5.6%)
Pacemaker + ASD	82(91.1%)
Outcome	
Seizure free	28 (31.1%)
Not seizure free/not specified	22 (24.4%)/40 (44.4%)
Syncope free	64 (71.1%)
Not syncope free/not specified	1 (1.1%)/25 (27.8%)

seizures despite treatment and 40 (44.4%) did not have documentation of their seizure control. In terms of syncope, 64 patients (71.1%) had no ongoing syncope after PM implantation, one patient (1.1%) continued having syncopal spells and in 25 patients (27.8%) this outcome was not specified.

Of the reviewed cases, epilepsy surgery was only performed in seven patients (7.8%). Six of these patients (6.7%) underwent surgery following PM implantation. Overall, five patients were able to have their PMs removed following epilepsy surgery and continue treatment with ASDs alone.

A review of 63 cases of IB demonstrated that the epileptogenic origin in 67% of patients was in the temporal lobe, with the remainder of cases originating in the frontal lobe. This review also found a left to right hemispheric origin ratio of 26 to 19 [1]. A review of 157 cases of IA found a mean asystole duration of 18 s, with a range of 3 to 96 s. All of the reviewed IA cases had focal epilepsy. Eighty to eighty-two percent of these IA cases were localized to the temporal lobe with 62% being lateralized to the left side. Seventy-five percent of IA cases had an abnormal EEG, with 43% of recordings showing focal activity and 57% showing focal to bilateral seizure activity. In 7% of the cases, IA developed during secondary tonic–clonic seizures. A majority of the IA cases (72%) met criteria for ASD resistance.

Many of the reviewed cases had abnormal neuroimaging, although none were described as having the extensive white matter changes seen in our patient. Abnormalities documented in a study of 13 patients with IB included bilateral mesial temporal sclerosis (2 patients), low-grade glioma (2 patients), unilateral periventricular nodular heterotopia (1 patient) and a coiled left internal carotid artery aneurysm with a subacute infarct in the left subinsular area (1 patient) [5]. A separate study reported that 55% of patients with IA had abnormal neuroimaging with hippocampal sclerosis or atrophy in 37%, neoplasm in 17%, developmental abnormality in 15%, traumatic lesion in 8% and cavernoma in 5% [3].

4. Discussion

This case of left temporal lobe epilepsy with IB and IA is unique as it clearly documents the occurrence of ictal arrhythmias, the utility of PM implantation and the resolution of these arrhythmias following temporal lobectomy in a longitudinal assessment of one patient. To our knowledge, this extensive pre- and post-surgical documentation has not previously been reported in the same patient. Our review of the existing literature revealed that the majority of patients with IB and IA have temporal lobe epilepsy. From a management perspective, PM implantation was found to significantly decrease syncopal episodes in the majority of reviewed cases. Additionally, epilepsy surgery was found to prevent ongoing ictal arrhythmias and allow most patients to have their PMs removed, although surgery was performed in a very small number of reviewed patients.

IB and IA have clinical significance due to their role in seizure-related falls, syncope and, possibly, in SUDEP [28]. These ictal arrhythmias are infrequently recognized, but prolonged periods of recording increase the likelihood of their detection. Ictal asystole was detected in 0.27–0.4% of patients with epilepsy on prolonged video-EEG telemetry and in 16% of epilepsy patients with ambulatory long term ECG [2]. Long-term cardiac monitoring studies have identified IB in 2.1% of seizures and in 37% of patients with epilepsy [2]. These detection rates are surprisingly high, given how infrequently IB and IA are recognized clinically in patients.

The pathophysiology of IB and IA remains unclear, although several mechanisms have been proposed. One possibility is that IB/IA occurs as a physiological response to apneic episodes. Numerous other hormonal and metabolic changes in patients with epilepsy are suspected to contribute to the development of ictal arrhythmias. Epileptiform activity also seems to affect the autonomic nervous system, causing activation of parasympathetic networks and inhibition of sympathetic networks. This increase in parasympathetic drive results in bradycardia through increased vagal nerve stimulation. The presence of left sided lateralization in most patients with IB/IA may be related to hemispheric differences in autonomic control [1]. A study of five patients with epilepsy who underwent insular lobe stimulation prior to temporal lobectomy found that stimulation of the left insular cortex caused bradycardia more frequently, while stimulation of the right insular cortex caused tachycardia [6]. A predominant role of the left cerebral hemisphere in parasympathetic modulation has also been demonstrated using functional MRI [7]. Given these findings, it is possible that treatments modulating autonomic nervous system outputs could be useful for managing ictal arrhythmias [13,16–20,22–26].

Current treatment options for IB and IA include ASDs, PM implantation and epilepsy surgery. In our review, we found that a majority of patients were medically managed with ASD monotherapy. An essential principle of medical management with ASDs is avoidance of drugs with potentially arrhythmogenic and negative ionotropic profiles, including caution with usage of sodium channel blockers including PTH, CBZ and LTG. However, analysis of the reviewed cases showed that CBZ and LTG, along with LEV and PTH were used most commonly. Information surrounding optimal ASD selection in the setting of ictal arrhythmias should be made available to physicians caring for these patients to avoid worsening these cardiac effects.

Management of IB and IA with PMs has not been performed in a standardized manner, as no guidelines currently exist. Some recommend PM implantation only in those who have drug resistant epilepsy, seizure-related falls and are not candidates for epilepsy surgery [3,9]. The presence of falls and/or syncope either preceding or during ictal activity is associated with significant morbidity, especially when they occur with a frequency of 3 or greater per week [9–15]. Asystole duration and candidacy for epilepsy surgery have also been recommended as criteria to decide whether PM implantation is warranted [4]. This recommendation stems from the observation that asystole lasting longer than 4–6 s is associated with syncope and ictal falls [4,30–35]. In our review, the average duration of IA was significantly higher than this range (15.6 ± 11.7 s), suggesting that many patients would benefit from pacing. A consensus regarding how long PMs should be left in place after epilepsy surgery is also lacking. It may be reasonable to wait two years after epilepsy surgery

before explanting PMs, similar to the two-year waiting period that is followed by some neurologists for ASD withdrawal after epilepsy surgery [53]. Of course, studies will be needed to assess the optimal timing of PM withdrawal post-surgically.

Guidelines are also lacking to advise physicians when to consider epilepsy surgery in these patients [8]. As mentioned above, a very small number of sampled cases underwent epilepsy surgery (seven patients) [29]. From this group, five patients were able to have their PMs removed following epilepsy surgery and continue treatment with ASDs alone [12, 15,27,35–39]. Although this data is based on a small number of patients, these results are encouraging and strongly suggest that epilepsy surgery should be considered in more patients with IB and IA who are good surgical candidates.

Control of ictal arrhythmias is critical for safety in patients with epilepsy, as these arrhythmias may play a role in the pathophysiology of SUDEP. However, strong clinical evidence linking SUDEP and IB/IA is currently lacking [40–52]. Data from animal studies suggests that brief periods of IB/IA lasting a few seconds are likely benign. However, these animal studies indicate that IA lasting for longer periods (tens of seconds to minutes) is associated with significant hypoxemia that may cause critical decreases in cerebral oxygenation and, potentially, death [2]. Despite these findings from animal research, a systematic review of IA in human patients found no association between IA and permanent brain injury or death [3]. This lack of permanent injury from IA may occur because asystole is a purely ictal phenomenon that does not extend into the postictal period as it does in suspected cases of SUDEP [3]. The relationship between IA and SUDEP clearly warrants further investigation, given the potentially lethal outcomes in affected patients. Long-term studies examining rates of SUDEP in patients with ictal arrhythmias managed with PMs and epilepsy surgery, compared to those managed with ASDs are desperately needed.

5. Conclusions

Our report describes a case of a patient with left temporal lobe epilepsy affected by IB and IA who achieved seizure control and resolution of his arrhythmias following temporal lobectomy. His IB and IA were successfully managed with the use of a PM preoperatively, and the PM was able to be uneventfully removed after surgery. Patients with IB/IA have been shown to be at increased risk of seizure-related syncope and falls. The relationship between IA and SUDEP is still unclear, with conflicting evidence from animal models and human studies. Further investigation into the pathophysiology of IB and IA and long-term outcomes using different treatment modalities is clearly needed to help formulate treatment guidelines for these patients. Findings from this review suggest that PM implantation and epilepsy surgery should be considered in patients with drug-resistant seizures associated with IB and IA. It is possible that managing these patients with PMs and surgery could potentially improve their longevityby reducing their risk of SUDEP.

Acknowledgements, disclosures, conflict of interest

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Ethics in publishing

SB, IS, MP, FT, IM, LH and JT were involved in drafting and reviewing the manuscript. AW and JT were the physicians involved with the case. All authors approved the final version of the manuscript. All authors followed the ethical standards of Elsevier.

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